Surgical Atrioventricular Valve Replacement With Melody Valve in Infants and Children

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Abstract: Background Pediatric patients with atrioventricular valve disease have limited options for prosthetic valve replacement in sizes <15 mm. Based on successful experience with the stented bovine jugular vein graft (Melody valve) in the right ventricular outflow tract, the prosthesis has been modified for surgical valve replacement in pediatric patients with atrioventricular dysfunction with the intention of subsequent valve expansion in the catheterization laboratory as the child grows. Methods and Results A multicenter, retrospective cohort study was performed among patients who underwent atrioventricular valve replacement with Melody valve at 17 participating sites from North America and Europe, including 68 patients with either mitral (n=59) or tricuspid (n=9) replacement at a median age of 8 months (range, 3 days to 13 years). The median size at implantation was 14 mm (range, 9-24 mm). Immediately postoperatively, the valve was competent with low gradients in all patients. Fifteen patients died; 3 patients underwent transplantation. Nineteen patients required reoperation for adverse outcomes, including valve explantation (n=16), left ventricular outflow tract obstruction (n=1), permanent pacemaker implantation (n=1), and paravalvular leak repair (n=1). Twenty-five patients underwent 41 episodes of catheter-based balloon expansion, exhibiting a significant decrease in median gradient (P<0.001) with no significant increase in grade of regurgitation. Twelve months after implantation, cumulative incidence analysis indicated that 55% of the patients would be expected to be free from death, heart transplantation, structural valve deterioration, or valve replacement. Conclusions The Melody valve is a feasible option for surgical atrioventricular valve replacement in patients with hypoplastic annuli. The prosthesis shows acceptable short-term function and is amenable to catheter-based enlargement as the child grows. However, patients remain at risk for mortality and structural valve deterioration, despite adequate early valvular function. Device design and implantation techniques must be refined to reduce complications and extend durability. Clinical Trial Registration URL: https://www.clinicaltrials.gov. Unique identifier: NCT02505074.

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ORIGINAL ARTICLE

Surgical Atrioventricular Valve Replacement With Melody Valve in Infants and Children

A Multicenter Study

See Editorial by Kim

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BACKGROUND: Pediatric patients with atrioventricular valve disease have limited options for prosthetic valve replacement in sizes <15 mm. Based on successful experience with the stented bovine jugular vein graft (Melody valve) in the right ventricular outflow tract, the prosthesis has been modified for surgical valve replacement in pediatric patients with atrioventricular dysfunction with the intention of subsequent valve expansion in the catheterization laboratory as the child grows.

METHODS AND RESULTS: A multicenter, retrospective cohort study was performed among patients who underwent atrioventricular valve replacement with Melody valve at 17 participating sites from North America and Europe, including 68 patients with either mitral (n=59) or tricuspid (n=9) replacement at a median age of 8 months (range, 3 days to 13 years). The median size at implantation was 14 mm (range, 9–24 mm). Immediately postoperatively, the valve was competent with low gradients in all patients. Fifteen patients died; 3 patients underwent transplantation. Nineteen patients required reoperation for adverse outcomes, including valve explantation (n=16), left ventricular outflow tract obstruction (n=1), permanent pacemaker implantation (n=1), and paravalvular leak repair (n=1). Twenty-five patients underwent 41 episodes of catheter-based balloon expansion, exhibiting a significant decrease in median gradient (P<0.001) with no significant increase in grade of regurgitation. Twelve months after implantation, cumulative incidence analysis indicated that 55% of the patients would be expected to be free from death, heart transplantation, structural valve deterioration, or valve replacement.

CONCLUSIONS: The Melody valve is a feasible option for surgical atrioventricular valve replacement in patients with hypoplastic annuli. The prosthesis shows acceptable short-term function and is amenable to catheter-based enlargement as the child grows. However, patients remain at risk for mortality and structural valve deterioration, despite adequate early valvular function. Device design and implantation techniques must be refined to reduce complications and extend durability.

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Key Words: bioprosthetic valve ■ heart valve prosthesis implantation ■ mitral valve ■ pediatrics ■ tricuspid valve

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WHAT IS KNOWN

- An externally stented bovine jugular vein graft is an expandable valve currently offered as an option for replacement of the right ventricular outflow tract.
- There are limited options for bioprosthetic valves in pediatric patients with atrioventricular valve annuli <15 mm.

WHAT THE STUDY ADDS

- The surgically modified and implanted externally stented bovine jugular vein graft offers acceptable short-term function in the atrioventricular valve position in pediatric patients.
- In addition, the surgically implanted externally stented bovine jugular vein graft is amenable to catheter-based expansion as the child grows.

Clinical and surgical management of atrioventricular valve disease in infants and young children remains a therapeutic challenge with high morbidity and mortality associated with valve replacement.[1–3] Mitral valve replacement (MVR), in particular, has proven to be challenging in this population with relatively high rates of reintervention.[2,4–11] A unique challenge is the lack of commercially available prosthetic valve replacement options for children with annuli <15 mm.

In the past decades, the development of new valve technologies has made the percutaneous replacement of dysfunctional valves possible.[12,13] The Melody valve (Medtronic, Minneapolis, MN) is a stent-mounted valved bovine jugular vein graft that is approved for transcatheter implantation into the right ventricular outflow tract position where it has been shown to restore pulmonary valve competence and relieve outflow tract obstruction, even in young patients.[14]

Based on its favorable design characteristics and initial success in the right ventricular outflow tract position, the Melody valve was adapted for atrioventricular valve replacement. Initial experience demonstrated the feasibility of MVR with the Melody valve in patients with annuli <15 mm.[15–18] Importantly, these studies demonstrated the valve could be expanded in the catheterization laboratory after somatic growth, thus avoiding early reoperation.

Following the initial studies, an increasing number of centers began offering Melody valve for atrioventricular replacement. Given the rarity of suitable cases, an international multicenter registry of atrioventricular valve replacement with the Melody valve was established in North America and Europe to allow for rapid accumulation of combined experience rather than a single-center effort. Thus, in the present study, we aim to report the current multicenter experience with Melody valve in atrioventricular position and to investigate the procedural short- and medium-term outcomes.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Patient Selection

A multicenter, retrospective cohort study was performed among patients who underwent atrioventricular valve replacement with the Melody valve in 17 pediatric cardiac programs in North America and Europe. Approval was obtained from the institutional review board at each center, with either waiver of informed consent or written consent obtained before data collection. Insertion of the Melody valve in the mitral and tricuspid positions was performed under off-label use designation in all centers.

Candidates for surgical Melody insertion typically included patients with annuli <15 mm, which is deemed too small for implantation of a traditional mechanical or bioprosthetic valve. Deidentified clinical and echocardiographic data, from the time of diagnosis until the most recent follow-up (if applicable), were sent to the lead site at Boston Children's Hospital for collection and analysis.

Data Collection

Collected data included basic demographic information, descriptive anatomic diagnoses, associated noncardiac or genetic anomalies, preoperative factors, surgical procedures performed, complications incurred at the time of surgery or during follow-up, and mortality. Procedural details, including valve modification and insertion techniques, were collected from operative reports.

Data collected from follow-up included gradient and degree of valvular regurgitation immediately after implantation, at hospital discharge, and at most recent follow-up. Performance of the Melody valve was assessed based on freedom from structural valve deterioration (SVD) defined as regurgitation classified as moderate or greater on echocardiography. The study was unable to discriminate between central regurgitation and regurgitation because of paravalvular leaks or stent fracture. Progressive development of transvalvular stenosis was not included within definition of SVD as increasing gradient with somatic growth was anticipated and prompted transcatheter valve expansion. For patients who underwent catheter-based expansion of the Melody valve, the time to first cardiac catheterization, interval between dilations, and total number of interventions for valve expansion were documented.

Outcomes

The primary outcomes evaluated were[1] SVD and valve replacement, and[2] mortality or orthotopic heart transplantation (OHT). An additional outcome limited to descriptive analyses included surgery for procedure-related complications.

Operative Procedure

For atrioventricular valve replacement, the technique for implantation has been described previously.[15–20] In most of the patients, a circumferential skirt of bovine pericardium was sewn externally to the stent at its midsection to facilitate fixation to the valve annulus. The circumferential skirt was sutured to the annulus with either interrupted or continuous sutures. After annular fixation, balloon dilation of the valve was performed (Figure 1). The balloon size was generally 1 mm greater than the anteroposterior valve annular measurement obtained by preoperative transthoracic or transesophageal echocardiography, as confirmed intraoperatively by ensuring passage of a similar-sized Hegar dilator through the annulus. Echocardiography was performed before discharge and at routine intervals to evaluate the progression of transvalvular gradient and regurgitation. Details of surgical procedure and prosthesis modifications were collected.

Catheter-Based Valve Expansion

A patient was deemed a candidate for re-expansion if the mean gradient across the prosthesis as measured by pulse wave Doppler increased with somatic growth to >10 mm Hg. At catheterization, femoral or jugular venous access was used to approach the valve. For mitral dilation, the left atrium was accessed through either a previously placed atrial septal defect or transseptal puncture (Figure 1F). The balloon size used for expansion was recorded and compared with the original balloon size used at implantation. Gradients across the prosthesis and regurgitation grade were recorded immediately before and after catheter-based expansion.

Statistical Analysis

Categorical variables are presented as proportions and continuous variables as mean±SD or median (interquartile range, minimum to maximum) as appropriate.

The median postoperative gradient and amount of regurgitation before and after balloon dilation were compared by nonparametric Wilcoxon signed-rank test and McNemar paired test, respectively. Overall mortality or OHT was analyzed using the Kaplan-Meier method.

Analysis of the cardiac catheterization data was conducted accounting for death or OHT as competing event.[21] A further competing risks analysis was conducted on the first occurrence, during follow-up of SVD or valve explantation, and death or OHT. Gray test was used to evaluate hypotheses of no difference of crude cumulative incidence functions between different techniques of valve modification and implantation, primary diagnosis, and quartiles of age at the time of surgery.

Median follow-up time was calculated according to reverse Kaplan-Meier method.[22]

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC). A 2-tailed $P \leq 0.05$ was considered statistically significant.

RESULTS

The study enrolled 68 patients who underwent surgical implantation of an expandable bovine jugular vein valve into mitral (n=59) or tricuspid (n=9) positions. Patient characteristics are outlined in Table 1.

The majority of patients were males (57%) with a median age at implantation of 8.6 months (range, 3 days to 14 years). Two patients were >8 years of age at the time of Melody valve implantation. In 1 case, the patient was unusually small for age (age, 12 years; weight, 7.8 kg) with a mitral valve annulus of only 12 mm. Similarly, in the second case, the patient had a diagnosis of Shone complex, and the mitral valve annulus was deemed too small for any available prosthesis. Indications for valve replacement included valvular regurgitation moderate or greater in 17 (mitral, n=11; tricuspid, n=6), valvular stenosis (moderate or greater) in 7 (mitral, n=5; tricuspid, n=2), and both regurgitation and stenosis in 44 (mitral, n=43; tricuspid, n=1) patients. Eleven (16%) patients had associated comorbidities, primarily genetic syndromes.

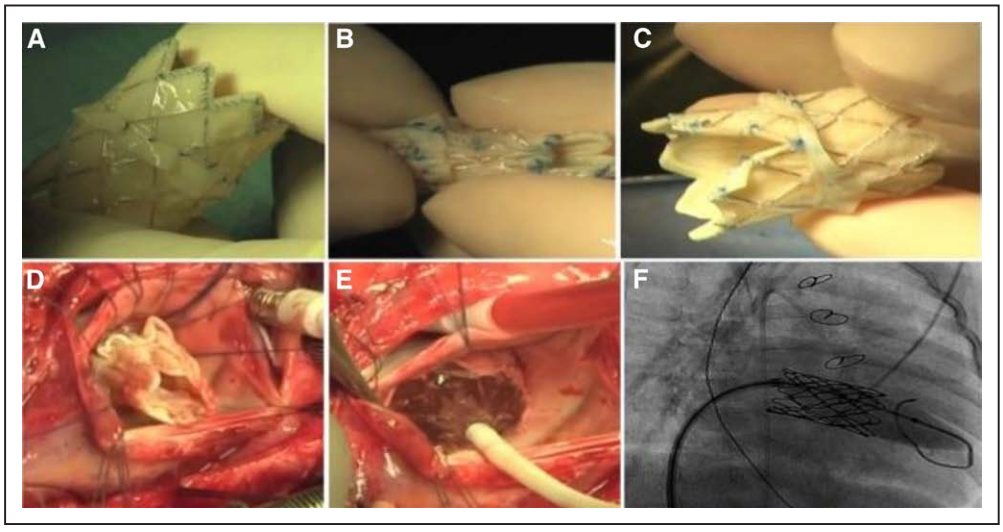

Figure 1. Steps of Melody valve preparation, surgical implantation, and intraoperative catheter balloon dilation.
A-**C**, Preparation of the valve; (**D**-**E**) implantation of the valve; (**F**) catheter balloon dilation of the Melody valve during follow up. Reprinted from Frigiola et al[26] with permission. Copyright ©2017, Europa Digital & Publishing.

Table 1. Demographic Data for n=68 Patients

Characteristics	Value
Age at diagnosis, mo; median (IQR)	8.6 (17.52)
Men, n (%)	39 (57)
Weight, kg; median (IQR)	6.6 (5.27)
BSA, m^2; median (IQR)	0.33 (0.19)
Fundamental diagnosis, n (%)	
Atrioventricular canal defect	19 (28)
Congenital mitral stenosis	12 (18)
Mitral regurgitation (congenital or acquired)	5 (7)
Congenital mitral regurgitation and mitral stenosis	19 (28)
Shone syndrome/complex	5 (7)
Hypoplastic left heart syndrome	3 (4)
Tricuspid regurgitation	2 (3)
Pulmonary atresia with intact ventricular septum	2 (3)
Native MV endocarditis	1 (1)
Comorbidities, n (%)	
Heterotaxy syndrome	3 (4)
Trisomy 21	3 (4)
Other genetic syndromes	5 (7)
Previous valve repair or replacement, n (%)	49 (72)
1 previous valve surgery, n	30
≥2 previous valve surgeries, n	19
Previously implanted prosthetic valve degeneration, n (%)	6 (9)

ASD indicates atrial septal defect; BSA, body surface area; IQR, interquartile range; and SVD, structural valve deterioration.

Table 2. Operative Techniques for Surgical Implantation of the Melody Valve With Postoperative Gradients and Long-Term Outcomes

Variables	Total (n=68)	Mitral (n=59)	Tricuspid (n=9)
Melody valve modification, n (%)	62 (91)	55 (93)	7 (78)
V shape, n (%)	13 (19)	13 (22)	0
Melody stent trimmed (distal), n (%)	26 (38)	22 (37)	4 (44)
Melody stent trimmed (proximal), n (%)	42 (62)	35 (59)	7 (78)
Addition of pericardial skirt, n (%)	42 (62)	38 (64)	4 (44)
Implanted with running sutures, n (%)	33 (48)	28 (47)	5 (55)
Implanted with interrupted sutures, n (%)	36 (53)	33 (56)	3 (33)
ASD creation, n (%)	17 (25)	17 (29)	0
Attachment to the free wall, n (%)	21 (31)	21 (35)	0
Balloon dilation size, mm; median (IQR)	14 (15)	14 (15)	16 (10)
Discharge gradient, mm Hg; median (range)	4 (0–16)	4 (2–7)	5 (1–9)
Discharge regurgitation grade, median (range)	None (none-trivial)	None (none-trivial)	None (none-mild)
Heart block, n (%)	10 (15)	8 (13)	2 (22)
Mortality, n (%)	15 (22)	11 (19)	4 (44)
In-hospital death, n (%)	8 (12)	7 (12)	1 (11)
Late death, n (%)	7 (10)	4 (8)	3 (33)
Cardiac transplantation, n (%)	3 (4)	2 (33)	1 (11)
Cardiac catheterization, total procedure, n (%)	41 (60)	2 (3)	1 (11)
1 cardiac catheterization procedure	25 (37)	24 (41)	1 (11)
≥2 cardiac catheterization procedures	16 (23)	16 (27)	0
SVD and valve re-replacement	19 (36)	17 (35)	2 (40)

ASD indicates atrial septal defect; and SVD, structural valve deterioration.

Gray test showed no difference of crude cumulative incidence functions (SVD or valve replacement and mortality or OHT) and age at the time of surgery or primary diagnosis (P=0.958 and P=0.724, respectively).

Most patients (72%) had undergone at least 1 previous surgical attempt to repair the dysfunctional atrioventricular valve, and 28% of the patients had >1 surgical valve revision before undergoing Melody valve implantation. Six (9%) patients had prosthetic valve dysfunction as indication for Melody valve implantation.

Procedural details, including valve modification and insertion techniques, are outlined in Table 2. In all but 6 patients, the Melody valve was modified before implantation. In 48 patients (mitral, n=41; tricuspid n=7), the valve was shortened by trimming or folding of the proximal or distal crowns.[19] In 13 (22%) patients with the Melody valve in mitral position, the prosthesis was further shortened before implantation by creating a deep V-shaped incision on the side facing the left ventricular outflow tract (LVOT) to prevent additional obstruction of the outflow. In 42 cases (mitral, n=38; tricuspid, n=4), a strip of pericardium was sutured around the exterior stent valve in a skirt to facilitate anchoring to the valve annulus. Fixation of the distal stent to the posterior wall of the left ventricle to prevent excessive device motion during the physiological annular systolic motion was performed in 21 patients who implanted the Melody valve in mitral position. The atrial septum, removed to allow access to the mitral valve from right atriotomy, was reconstructed with patch material and fenestrated to allow future catheter access to the prosthesis in 17 cases. Once sutured to the native valve annulus, the Melody valve was expanded with a balloon catheter to reach the desired diameter. The balloon size utilized for initial valve expansion was a median of 14 mm (range, 9–24 mm).

Nine (13%) patients developed various degrees of transient heart block immediately after implantation, including 8 patients who underwent MVR and 1 who underwent tricuspid valve replacement. Permanent pacemaker was documented only in 1 patient. One patient with hypoplastic left heart syndrome underwent pacemaker implantation at time of Melody valve implantation for preexisting complete heart block.

The median duration of hospitalization was 21 days (range, 6–722 days).

At discharge, the mean echocardiographic Doppler gradient of the Melody in mitral position was 4 mm Hg (interquartile range, 5 mm Hg; full range, 0–16 mm Hg), and regurgitation was mild or less in 54 (98%) patients. The median value of the mean gradient of the Melody valve in tricuspid position at discharge was 5 mm Hg (interquartile range, 8 mm Hg; full range, 0–12 mm Hg), and regurgitation was mild or less in 8 (86%) patients (Table 2).

The mean follow-up time was 23 months (range, 2 days to 4.7 years) for the entire cohort.

The Kaplan-Meier estimated freedom from mortality or OHT was 81% (70%–89%) at 6 months, 76% (63%–85%) at 12 months, and 72% (58%–81%) at 24 months (Figure 2).

In total, 15 deaths occurred, including 11 in patients who underwent MVR (8 in-hospital and 3 late deaths) and 4 in those who underwent tricuspid valve replacement (all late deaths). Six of the 15 deaths occurred in patients receiving extracorporeal membrane oxygenation assistance for severe ventricular dysfunction. In these cases, the Melody valve was successfully implanted as salvage therapy in critically ill patients; however, only 1 of them recovered, whereas 6 died from multiorgan failure, despite having a functional valve prosthesis. Three patients (mitral, n=2; tricuspid, n=1) underwent OHT at 2, 3, and 3.8 months after Melody valve implantation. In each of these patients, transplantation was the intended long-term therapy, and valve replacement was performed as a bridge to planned transplantation.

The median gradient of the Melody valve on the most recent follow-up echocardiogram was 7.5 mm Hg (interquartile range, 17 mm Hg; full range, 0–22 mm Hg), and regurgitation was mild or less in 82% of the patients. As gradients were measured only at the most recent follow-up, as opposed to multiple testing points, trends could not be assessed over time. Nineteen (28%) patients, 17 in the mitral position and 2 in the tricuspid position, showed clinically worsened valvar regurgitation (moderate or severe) during follow-up. All but 2 had extensive valve modification (V shape in 4 patients, trimming or bending in 12 patients, and skirt addiction in 11 patients). Gray test of difference showed no evidence of correlation between adverse events (SVD or valve replacement, and mortality or OHT) and surgical implantation techniques, such as resection of the valve stent and graft (proximal, distal, and sinus facing the LVOT), or type of sutures performed.

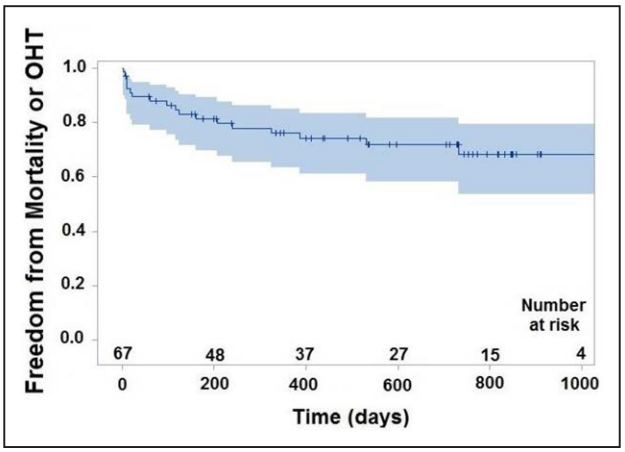

Figure 2. Kaplan-Meier curve with 2-sided 95% CIs depicting freedom from mortality or orthotopic heart transplantation (OHT).

During follow-up, a subgroup of 25 (37%) patients (mitral, n=24; tricuspid, n=1) with increasing transvalvular gradient underwent balloon dilation for expansion of the Melody valve. The median time to first balloon dilation was 6.9 months after implantation (range, 7 days to 2.8 years). Ten patients with Melody in mitral position had >1 balloon dilation, for a total of 41 procedures. After cardiac catheterization, median transvalvular gradient decreased significantly from before to after balloon dilation (Wilcoxon rank-sum test, $P<0.05$; Figure 3A). The grade of valvular regurgitation was not significantly different before and immediately after balloon dilation (Figure 3B).

Reoperation was performed in 19 (32%) patients, including 16 patients (all MVR) who underwent valve re-replacement. Reasons for valve re-replacement were endocarditis in 2 patients, SVD without evidence of endocarditis or blood stream infection in 6, Melody valve stenosis in 2, stent fracture in 2, and perivalvular leak in 1 patient.

Nonexplantation cardiac reoperations were performed in 3 patients, including 1 patient who underwent reoperation for relief of LVOT obstruction that developed after valve implantation, 1 patient who underwent epicardial pacemaker leads implantation, and 1 patient who underwent surgical closure of a paravalvular leak. Transient obstruction occurred immediately after the procedure in 7 (10%) patients secondary to the protruding stent. However, LVOT obstruction improved over time in 5, and only 2 (3%) patients required subaortic membrane resection. In 2 patients with LVOT obstruction, tilting of the distal portion of the Melody valve stent into the outflow tract contributed to obstruction and resulted in catheter-based interventions followed by reoperation. In 1 patient, the valve was eventually replaced; in the other, the Melody valve was expanded through a balloon catheter during surgery to relieve LVOT obstruction,

In 4 patients who developed central regurgitation and underwent Melody valve explantation, the valve showed perforation in one of the leaflets on surgical inspection (Figure 4). One of these patients developed central regurgitation 5 months after implantation, and on gross surgical examination, an injury related

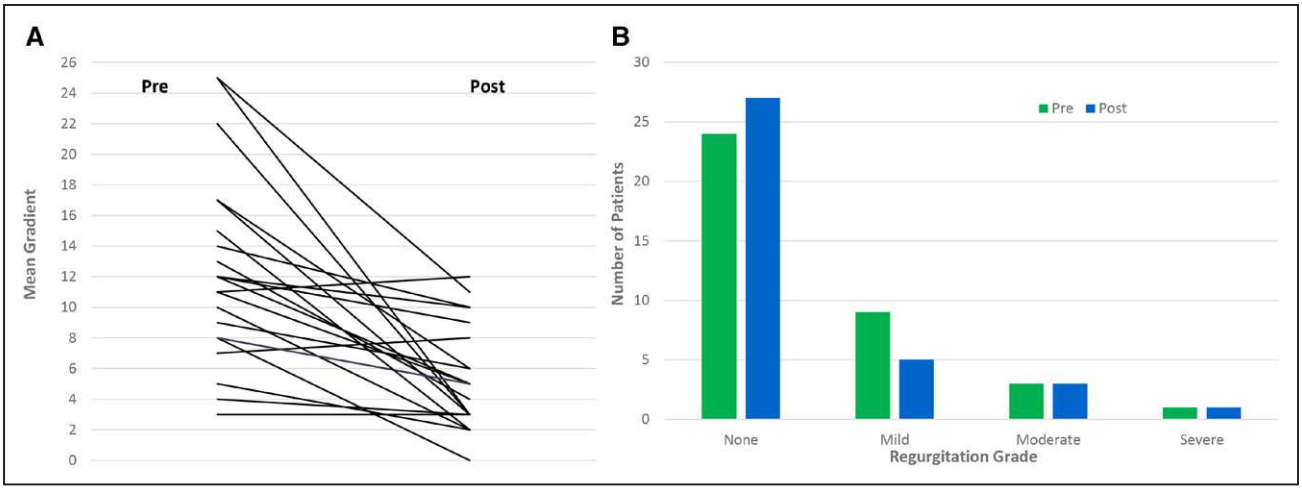

Figure 3. Transvalvular gradient and regurgitation immediately before and after balloon dilation of the valve.
A significant reduction in transvalvular gradient is seen (*P*<0.001; **A**). The grade of regurgitation was not significantly different before and immediately after balloon dilation (**B**).

to suture placement at the time of implantation was suspected. Another patient was lost at follow-up and was readmitted to the hospital with severe SVD. In this child, the histological examination of the valve showed signs of leaflet calcification and inflammation suggesting suspected endocarditis. In the remaining 2 patients, the degeneration of the valve was unknown because history and signs of endocarditis were not found. Leaflet morphology and histology examined in 3 of those 4 patients undergoing valve excision at 3, 12,[17] and 26 months after implantation demonstrated thin leaflets without evidence of leaflet calcification or inflammation.

In 1 patient, who died 13 months after Melody valve implantation because of an acute septicemia most probably not related to endocarditis, the valve was stable with only mild regurgitation without any relevant inflow gradient on echocardiogram. Histopathologic workup demonstrated complete neoendothelialization and only little neointimal formation, no signs of calcification, and loosely inflammatory reactions with no macrophages or granulocytes confirming the good biocompatibility of the valve.[23]

Competing Risks Analyses

Within 2 years after Melody valve implantation, the crude cumulative incidence of death as first event was 28% (17%–39%; Figure 5A), whereas the crude cumulative incidence of valve re-replacement or SVD as first event was 20% (11%–32%; Figure 5B).

Considering Melody SVD or valve explantation and mortality or OHT as competing events, the estimated probability of experiencing one of the adverse events is 28% (18%–40%) during the first year and 45% (32%–58%) within 2 years after Melody valve implantation (Figure 5C). The highest incidence of adverse events was in the first month after the procedure and is mostly comprised of death (Figure 5C).

Regarding cardiac catheterization, the estimated crude cumulative incidence was 17% (8%–27%) at 6 months, 18% (10%–29%) at 12 months, and 23% (13%–35%) at 24 months (Figure 6).

DISCUSSION

This study presents a multi-institutional experience with feasibility, safety, and clinical efficacy of the surgical

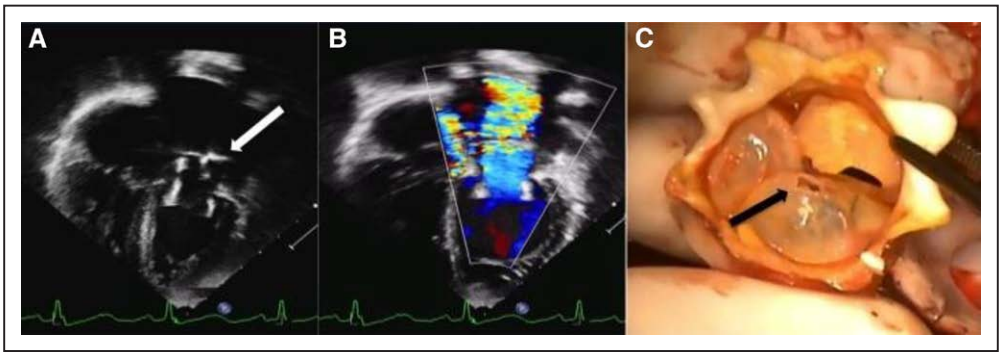

Figure 4. Gross examination of an explanted Melody valve from a patient 26 mo after implantation in the mitral position.
Follow-up echocardiogram showed abnormal prolapse of 1 leaflet of the Melody valve (**A**, white arrow) conditioning massive valve regurgitation (**B**). The explanted valve showed injury to leaflet (**C**, black arrow) with thin leaflets and no evidence of inflammation or calcification.

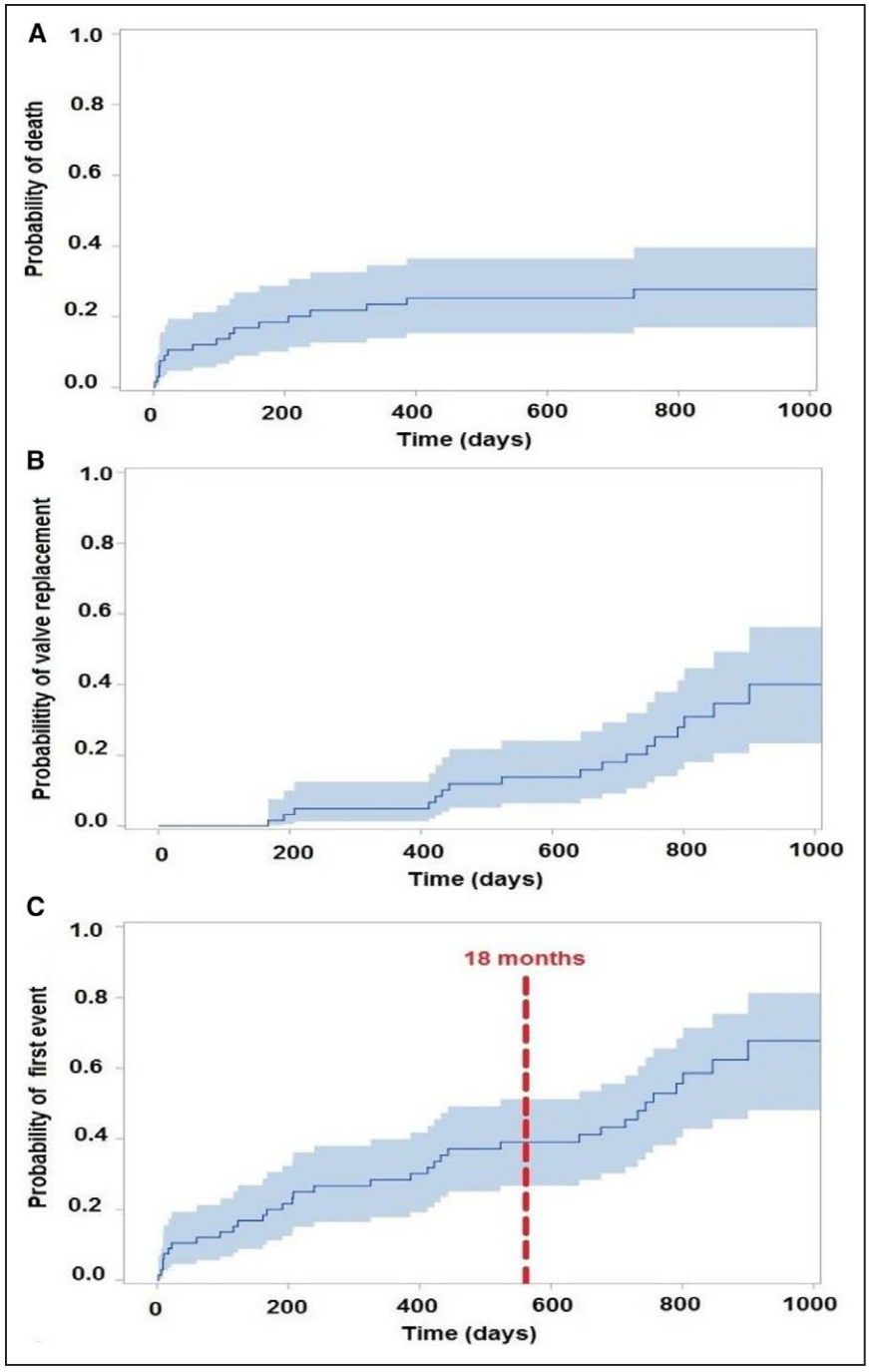

Figure 5. Estimated cumulative incidence curves with 2-sided 95% CIs.
A, Mortality or orthotopic heart transplantation. **B**, Structural valve deterioration or valve replacement. **C**, The combination of these 3 events.

implantation of the Melody valve in the atrioventricular position for the treatment of dysfunctional atrioventricular valve in pediatric patients with hypoplastic annuli. The results indicate that there is a high rate of procedural success but high mortality in patients supported with extracorporeal membrane oxygenation. Medium-term follow-up showed that the Melody valve can be effectively balloon expanded to account for patient somatic growth. However, SVD and need for reoperation remain significant challenges with the current design.

Despite the significant advances in the management and treatment of complex congenital heart defects, surgical repair of atrioventricular valve dysfunction in children still carries a high mortality risk.[1–3] In the pediatric population, valve repair surgery is preferred and feasible in most patients; however, in patients with irreparable atrioventricular valves, valve replacement is the only option.

There are numerous concerns associated with prosthetic valve replacement in children. First, the small atrioventricular annulus in children limits the prosthetic options, considering that available prostheses range from 15 to 27 mm in diameter. Second, the growth of the atrioventricular annulus at small ages is exponential,

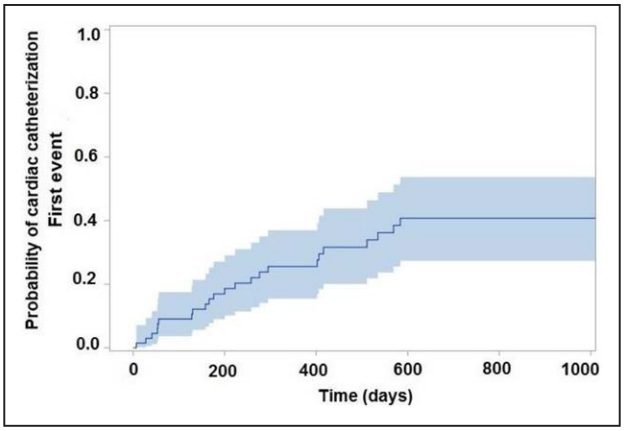

Figure 6. Estimated cumulative incidence curves with 2-sided 95% CIs of cardiac catheterization as first events in those who survived surgery.

and a fixed-sized prosthesis cannot accommodate for somatic growth of the patient. Thus, children who undergo valve replacement at a younger age require early reoperation to upsize the valve. Whereas bioprostheses tend to degenerate rapidly in young patients, mechanical prostheses require anticoagulation, which can be difficult to regulate in children.[24]

In this setting, the concept of an expandable prosthetic valve is appealing. Conceived as a temporary device to replace failing pulmonary valves, the Melody valve has shown adequate performance even under systemic pressures encountered in pulmonary hypertension.[25] In recent years, it has been used in a small cohort of pediatric patients for the treatment of dysfunctional mitral valves with promising results.[16,19,26] Feature that makes the stented bovine jugular vein graft optimal for valve replacement in children is the redundancy of the valve leaflets, which allows coaptation to occur on a range of diameters between 10 and 22 mm. After implantation at a small diameter, the valve may be subsequently balloon expanded by cardiac catheterization as the patient grows, thus delaying the need for reoperation. The thin stent structure minimizes the difference between the external support and internal diameter thus optimizing the effective valve orifice area.[27]

In the current cohort of patients, Melody valve implantation significantly improved inflow obstruction and valve regurgitation. Improvement in regurgitation has been shown to correlate with better outcomes especially after mitral valve surgery in children.[28] However, a significant number developed SVD of the Melody valve and required reoperation at median of 22 months after implantation. The underlying cause of SVD included endocarditis, paravalvular leak, and central valvular regurgitation because of leaflet perforation or noncoaptation. Although valve modification techniques were not statistically significantly associated with SVD, it is possible that surgical manipulation of the valve contributed to SVD. And because of this, it is ideal to avoid modifications to the valve when possible. However, in some cases of patients with small valve annuli, the inclusion of modifications (such as the deep V cut or trimming of the stent) is necessary to avoid left ventricular outflow tract obstruction. Because the valve is not designed for surgical implantation, paravalvular leak at the interface between the stent and annulus may occur. Improvements in valve implantation technique occurred during the course of the study, leading to reduction in the rates of SVD over time. Improvements in valve design, specifically tailored for surgical implantation, may further decrease the incidence of SVD.

Endocarditis has been reported after transcatheter Melody valve implantation.[29] In our cohort, endocarditis or blood stream infection was documented only in 2 patients. However, in case of SVD, a high index of suspicion for infective endocarditis should be always raised. Patients should be advised to follow lifelong antibiotic prophylaxis before surgical or dental procedures, and surgical management should not be delayed after Melody valve dysfunction.

Inflammation or calcification has been noted in explanted Melody valves, primarily demonstrated as pannus formation on the vein graft outer wall. However, remarkably, there is limited involvement of the leaflets in general, and they remain pliable for a significant span of time. The leaflets seem to be somewhat protected by the vein wall graft, which shields the internal leaflets. It is rare but certainly possible to develop pannus on the leaflets, and they can in fact develop a fibrous film as in the case with other bioprostheses. Because of the potential fibrotic response of utilizing a xenograft, the Melody valve is not intended to be a lifelong solution. Importantly, these explanted valves represent the select group of patients with valve failure.

Considering mortality, valve replacement, and cardiac catheterization as adverse events during follow-up, the highest incidence of adverse events occurred during the first month after surgery and was mostly comprised of death. All but one of the early deaths occurred in patients who required perioperative extracorporeal membrane oxygenation assistance because of ventricular dysfunction, despite the technical success of the procedure. Patients with late mortality exhibited various combinations of complex congenital heart defect, ventricular noncompliance, arrhythmias, and pulmonary hypertension. Valve disease in children and infants is a marker for underlying cardiac comorbidity, and this study demonstrates that valve replacement alone may not be sufficient to alleviate cardiac-related mortality in this population.

Timing of atrioventricular valve replacement in pediatric patients is highly variable and may impact survival.[2,7] Given the current prosthetic options for valve replacement, clinicians may medically manage young patients with significant valvular disease, resorting to

surgery only after progressive clinical deterioration. It can be speculated that in these patients, earlier surgical replacement might have mitigated the severity of dysfunction and improved survival. The availability of a durable expandable valve may allow clinicians to intervene earlier in the clinical course, before the development of irreversible injury. The need for valve replacement may also be a marker for ventricular noncompliance and dysfunction, which are not altered by valve replacement alone.

The ideal candidate for Melody valve in the atrioventricular valve position is the patient with irreparable atrioventricular valve and annular size <15 mm. The goal of valve replacement with Melody valve is to provide valvular competence until a child can receive a traditional prosthesis (>19 mm), by serial dilation over time. Many of the patients in this study who underwent repeat replacement late after Melody valve implantation were able to receive traditional prosthesis. Based on the durability data presented in this study, it is unlikely that the Melody valve will last until adulthood. Given the currently available options for bioprosthetic and mechanical valve replacement, we cannot recommend use of the Melody valve for patients with annulus size >19 mm. For patients with annuli between 15 and 19 mm, another option for atrioventricular replacement is 15 or 17 mm mechanical prosthesis or supra-annular implantation of larger mechanical valves. However, increased risk of atrial noncompliance and valve thrombosis has been reported with supra-annular implantation.[7] Future studies are necessary to compare the durability of Melody valve with 16 or 17 mm mechanical valves.

Considering that in 9% of our patients the indication for Melody valve replacement was mechanical valve dysfunction, Melody valve should be contemplated also as a bailout option for mechanical valve thrombosis that is in patients with hypercoagulability states or bleeding issue under anticoagulation. Current recommendations for anticoagulation after Melody valve replacement have not yet been validated but based on previous studies suggesting low risk of thromboembolic events at short-term follow-up alone is currently recommended.[17] Long-term data on thromboembolic complications, such as stroke and limb ischemia, will be necessary to determine optimal therapy.

Optimal valve sizing of the Melody valve at the time of implantation has yet to be established. The protocol for implantation followed by participating centers was based on previous experience.[30] None of the patients sustained coronary artery damage, and only 1 (1.5%) patient developed complete heart block requiring pacemaker implantation. This incidence of heart block is lower than previously reported with mitral annulus upsizing in children,[31] highlighting the potential benefit of the Melody valve that can be dilated after somatic growth of patients. However, cardiac catheterization is not free of adverse events, and the risk of coronary artery injury, heart block, and left ventricular outflow tract obstruction associated with excessive valve dilation at the time of surgery must be weighed against the need for early catheterization associated with less-aggressive expansion.

The Melody valve stent is ≈28 mm long, which occupies significant space within the atrial and ventricular chambers and may potentially result in obstruction of the venous return or ventricular outflow tract. To prevent these complications, most of the centers modified the valve by either stent trimming or folding. In this series, inflow and outflow tract obstruction after Melody valve placement was a rare occurrence. No direct relationship was found between Melody valve failure and valve modification at implantation. However, it should be taken into account that excessive valve modification can be responsible for SVD during the follow-up. In particular, stent fractures remain the most common reason for reintervention with the Melody valve in pulmonary position because they are associated with early conduit restenosis and valve failure.[26] In our series, documented mechanisms of SVD in patients who underwent valve re-replacement included damage of the thin conduit wall during valve preparation, surgical injury of a valve leaflet during the valve modification, and penetration of the valve leaflets during balloon-catheter expansion of the prosthesis. Further customization of valve design for surgical atrioventricular valve replacement may reduce the need for valve modifications and thereby improve durability.

The median interval between surgery and the first catheter-based dilation was ≈6.5 months. It is important to note that because the gradient measured by echocardiography can differ from the gradient measured by catheterization, thus change in the echocardiographic gradient rather than a threshold value should be used to determine the timing of catheterization. Catheter-based dilation was well tolerated in most patients without development of more that mild regurgitation. The results demonstrate that valve expansion after somatic growth is feasible, allows relief of gradient across the valve, and delays reoperation for repeat valve replacement.

CONCLUSIONS

Although the mortality and adverse event profile for Melody valve placement in the atrioventricular valve position in pediatric patients is similar to other valve alternatives, there remain many potential benefits to this technology. First, the valve may be tailored to annuli that are too small for currently available prostheses avoiding supra-annular placement. Next, the Melody valve may be expanded in the catheterization laboratory to accommodate somatic growth thus avoiding repeat surgery. Finally, it avoids the complexity of anticoagulation in

small children and the associated complications of anticoagulation. Despite these things, many of the patients in this cohort were implanted with the Melody valve as a salvage therapy, thus there are still some noted negative outcomes (ie, risk of endocarditis) and an overall mortality of 22%. Perhaps the risk can be reduced if the valve is replaced sooner. Although further studies are needed to optimize patient selection, future design modifications are necessary to improve durability and expand applicability to the most challenging patients.

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